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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/791,017	OBENDORF ET AL.	
	Examiner	Art Unit	
	Zachary C Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 12-30* is/are pending in the application.

4a) Of the above claim(s) *12,13 and 19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 14-18 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/22/04; 8/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 1/11/2005 are acknowledged. Claims 1, 3, 6, 14, and 15 have been amended. Claims 10 and 11 are canceled. Newly submitted claims 23-30 are added.

Election/Restrictions

2. Applicant's election of Group I, claims 1-9 and 14-18, in the reply filed on 1/11/2005 is acknowledged. Applicant did not indicate whether the election was with or without traverse, but because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Therefore the restriction is deemed proper and is made FINAL.

Applicant indicates in the reply filed 1/11/2005, that the newly filed claims 23-30 depend from Group I claims and are thus Group I claims. Newly submitted claims 23-25 and 28-30, which depend respectively from Group I claims 1, 3, 6, 14, 15 and 1, are acknowledged as belonging in Group I. However, newly submitted claims 26 and 27 depend from claim 12, which is a Group II claim, and therefore belong in Group II, by original presentation.

Claims 12, 13, 19-22, 26 and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of the species of 1) nerve cells and 2) RT-PCR measuring method in the reply filed on 1/11/2005 is acknowledged.

Claims 1-9, 14-18, 23-25 and 28-30, in so far as they are drawn to the elected species, are under consideration.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

It is noted that the instant application claims priority to the U.S. Provisional Application 60/465692, filed April 25, 2003. However, said provisional application is written in German. Priority to the filing date of said document will not be given unless Applicant provides an English translation.

Specification

The disclosure is objected to because of the following informalities:

When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and a sequence identifier ("SEQ ID NO:X") must be used either in the drawing or in the Brief Description of the Drawings. See MPEP 2422.02. In the instant application, a sequence identifier must be used for the sequences appearing in Figure 3.

According to 37 CFR 1.821(d) (MPEP § 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences appear on page 8, line 23, ("...LXXLL...") of the specification but are not identified by SEQ ID NO as required.

Appropriate correction is required.

Claim Objections

Claim 1 is objected to because of the following informalities: For clarity, the term substances in claim 1 should be amended to read "a test substance".

Claims 3 and 6 are objected to because of the following informalities: The method steps presented in the claims should be amended follow the method steps of claim 1, from which claim 3 and 6 each depend (via claim 2, which presents no additional method steps). For example, as currently written (a) and (b) of claim 3 should be amended to read (d) and (e).

Claim 5 is objected to because of the following informalities: the phrase "...wherein said cells are eukaryotic cells and said eukaryotic cells selected from..." is redundant and should be amended to "...wherein said cells are eukaryotic cells selected from..."

Claim 6 is also objected to because of the following informalities: The recitation in line 6 of the claim of "...and are transfixed with a reporter gene construct" should be amended to read "...and wherein said cells are transfixed with a reporter gene construct". The recitation in line 7 of "...and ligands..." should be amended to read "...and with ligands..." The recitation in line 8 of "...measuring reporter..." should be amended to read "...measuring said reporter..."

Claim 17 is objected to because of the following informalities: The recitation in the claim of "...sequence region 8 to 2032..." should be amended to "...sequence region 8 to 2032 of SEQ ID NO: 1..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 14-18, 23-25 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of determining the effect of a test substance on the binding, or ligand-induced activity, of an Ewing sarcoma protein of SEQ ID NO: 2, or a fragment of said protein comprising amino acids 319-656, and a naturally occurring human androgen receptor, or a fragment of said receptor comprising amino acids 325-918, or a hepatocyte nuclear factor-4 (HNF-4) as taught by Araya et al, 2003 (cited on the IDS submitted 8/4/2004),

does not reasonably provide enablement for said method using other derivatives of a Ewing sarcoma protein of SEQ ID NO: 2, or with other derivatives of a naturally occurring human androgen receptor, or for said method performed in vivo. Claims 15-18 and 29 are also lack enablement for a method using a nucleic acid that is not expressed, and for a method that does not include the androgen receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a method of screening for test substances that alter the interaction between an Ewing Sarcoma Protein (EWS) and an androgen receptor (AR). The specification discloses two ways in which interactions between EWS and AR can be detected. First, in a yeast two-hybrid assay, a fragment of EWS consisting of amino acids 319-656 of SEQ ID NO: 2 interacts with a fragment of AR consisting of amino acids 325-918 of a naturally occurring human AR (page 19 of the specification). Second, full length EWS with a sequence of SEQ ID NO: 2 stimulates the androgen-induced activity of the full-length human androgen receptor to a higher degree than androgen alone (page 20, line 11 to page 21, line 10, and also Figure 4).

The breadth of the claims is such that the claims encompass a very broad genus of EWS polypeptides and also a very broad genus of AR polypeptides. Independent claims 1, 14, and 15 are drawn to a method using EWS, or a derivative of EWS, and AR. Claim 1 also includes derivatives of AR. The term "derivative" is defined on page 5 of the specification as including any variant of the protein "obtained by amino acid deletion, substitution, insertion, inversion, addition or exchange." While the specification

(same page) indicates that functional derivatives (defined as having "the ability to influence the activity of other proteins") are a preferred embodiment, neither the specification nor any of the claims limit the genus of polypeptides to any particular functional characteristics. Therefore, claims 1-9, 14-16, and 23-25 and 28-30 encompass any possible derivative of a EWS and/or AR, including those with highly divergent sequences in which most or all of the polypeptide is replaced with a sequence from a different polypeptide, with no limitation that the derivative must retain the same functional properties as an EWS of SEQ ID NO: 2 or a naturally occurring human AR. Claims 17 and 18 encompass a EWS encoded by any polynucleotide with 70% sequence identity to SEQ ID NO: 1, or with 70% sequence identity to nucleotides 8-2032 or 1000-2001 of SEQ ID NO: 1.

Claims 1-9, 14-18, 23-25 and 28-30 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides will retain the characteristics of an EWS of SEQ ID NO: 2, or a naturally occurring human AR. Applicant has not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, beyond the single example of the fragments described above. For example, applicant has not defined a difference in structure, or a difference in function, between the protein corresponding to SEQ ID NO: 2 and derivatives of a EWS protein. If a variant of the protein corresponding to SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, than the specification has failed to teach how to use such a variant.

Furthermore, the specification (on page 8, lines 14-15) teaches that "rearranged EWS fusion proteins have lost the ability to bind to the androgen receptors".
As the encompassed EWS derivatives include an unlimited number of substitutions and additions, the claimed genus of EWS proteins encompasses these non-functional fusion proteins.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification (page 5) indicates that derivatives of EWS or AR can be produced by modifications to the amino acid sequence of the proteins, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel

applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations other than broad fragments of hundreds of amino acids, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 1-9, 14-18, 23-25 and 28-30 are further not enabled in a manner commensurate in scope with the claims because they are directed to methods of testing the effect of a substance on the interaction between EWS and AR, but said methods are not limited to isolated proteins or cells, and therefore encompass said methods performed in vivo. No working or prophetic examples of said methods performed in vivo are provided in the specification. It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether the method of the present invention could be used in vivo. The specification does not teach that the EWS protein and the AR receptor interact in vivo, and it is not clear whether the test substance, androgen, EWS, and the AR receptor could be brought together in vivo in such a manner that they would interact. The specification fails to teach the skilled artisan how to use said method in vivo without resorting to undue experimentation to determine whether or not it actually works. The

specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use said method for the above stated purpose.

With respect to claims 15-18 and 29, the claims also lack enablement for a method using a nucleic acid that is not expressed. The claims as written encompass a method wherein a nucleic acid is used but not expressed, i.e., a method with a nucleic acid present but no EWS protein present. No examples of such a method are provided in the specification, and it is not predictable that such a method would work. In order to practice the invention as claimed, undue experimentation would be required by a skilled artisan to determine whether said method would work or not.

Claims 15-18 and 29 also lack enablement because the claims as written do not require an androgen receptor. No examples of a method "for identification and characterization of substances that influence androgen receptor activity" in the absence of an androgen receptor are provided in the specification, and it is not predictable that such a method would work. In order to practice the invention as claimed, undue experimentation would be required by a skilled artisan to determine whether said method would work or not.

Claims 1-9, 14-18, 23-25 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method for screening the effect of a test substance on the interaction between an Ewing Sarcoma Protein (EWS), or a derivative of an EWS, and an androgen receptor, or a derivative of an androgen receptor. Independent claims 1, 14, and 15 specifically refer to derivatives of EWS and/or the androgen receptor. The term "derivative" is defined on page 5 of the specification as including any variant of the protein "obtained by amino acid deletion, substitution, insertion, inversion, addition or exchange." While the specification (same page) indicates that functional derivatives (defined as having "the ability to influence the activity of other proteins") are a preferred

embodiment, neither the specification nor any of the claims limit the genus of polypeptides to any particular functional characteristics. Therefore, claims 1-9, 14-16, and 24-30 encompass any possible derivative of a Ewing Sarcoma Protein (EWS) or androgen receptor (AR), including those with highly divergent sequences, and with no limitation that the derivatives must retain the same functional properties as a Ewing Sarcoma Protein of SEQ ID NO: 2, or a naturally occurring human AR. Claims 17 and 18 encompass any EWS encoded by a polynucleotide with 70% sequence identity to SEQ ID NO: 1, or 70% sequence identity to nucleotides 8-2032 or 1000-2001 of SEQ ID NO: 1, e.g. sequences from other species, mutated sequences, or allelic variants. Thus each genus of polypeptides (the genus EWS proteins and the genus of AR proteins) is highly variant because a significant number of structural differences between genus members is permitted. While the claims do not specifically include any functional characteristics that must be present in the polypeptides, in order for the method to be performed as claimed, the variant EWS proteins and the variant androgen receptors must be able to interact with each other.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides, to describe the essentially limitless genera encompassed by the claims. The instant disclosure of a single EWS polypeptide of SEQ ID NO: 2, encoded by a polynucleotide of SEQ ID NO: 1, and a fragment consisting of amino acids 310-656 of SEQ ID NO: 2 that can bind AR, does not adequately support the scope of the claimed genus of EWS derivatives. Similarly, the instant disclosure of a single AR polypeptide, that of naturally occurring human AR, and a fragment consisting of amino acids 325-918

that can bind EWS, does not adequately support the scope of the claimed genus of AR derivatives. While the specification indicates that a fragment of EWS and a fragment of AR can interact in a yeast two-hybrid assay, the specification and claims do not provide any other guidance as to what changes could be made, and still retain the ability of EWS and AR to interact. Structural features that could distinguish polypeptides in the genus from others that do not interact are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. There is no description of the conserved regions that are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Missing from the disclosure are structural features that could distinguish EWS and AR proteins in the genus from EWS and AR derivatives that do not interact. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides and polynucleotides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the chemical structure of encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of description for that broad class. The specification provided only the bovine sequence.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. a EWS polypeptide that is homologous to SEQ ID NO: 2 and has the function of the parent polypeptide, or an AR polypeptide that is homologous to a naturally occurring human AR and has the function of the parent polypeptide. Thus, with the exception of the EWS polypeptide of SEQ ID NO: 2, or a derivative consisting of amino acids 319-656 of SEQ ID NO: 2, a naturally occurring human AR receptor, or a derivative consisting of amino acids 325-918, the skilled artisan cannot envision encompassed variants. Therefore, only said polypeptides, but not the full breadth of the claims, meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 14-18, 23-25 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Claim 1 is missing a conclusion

step that leads to the identification required by the preamble (i.e., "determining the hormonal effects of substances"). It is unclear how "determining the effect of the test substance on binding of said Ewing sarcoma protein with said androgen receptor" leads to the identification required by the preamble. Clarity could be added to the claim by adding at the end a phrase such as, "wherein a hormonal effect of a test substance is indicated by a _____ (e.g., an increase or decrease) in binding of said EWS with said AR in response to the test substance as compared to similar cells in the absence of the test substance..." Note that there must be basis in the specification for the type of response and the suggestions made by the examiner do not necessarily have basis but are intended to present the general idea of concepts that may be suitable. Claim 3 is rejected for the same reason as claim 1. Claim 30, which depends from claim 1, is also rejected because it does not remedy this situation. It is unclear how measuring concentrations of said androgen receptor and said Ewing sarcoma protein in claim 30 will lead to the identification required by the preamble of claim 1.

Claims 1, 14 and 15 are indefinite because the metes and bounds of the term "activity" are unclear. Neither the specification nor the art provide a single meaning for the term so that the skilled artisan would understand the breadth of the term.

Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Claims 14 and 15 do not contain any method steps that lead to the identification required by the preamble. It is not clear what is meant by the term "characterization". The specification does not define the term, and it is unclear what is intended to be encompassed by the term. Therefore, the claims are missing essential method steps that indicate how the characterization will be performed. Claims 28 and 29, which depend from 14 and 15 respectively, are also rejected because they do not remedy this situation. It is unclear how measuring concentrations of said androgen receptor and said Ewing sarcoma protein in claims 28 and 29 will lead to the identification required by the preamble of claim 14 and 15, respectively.

Claim 15 is also rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: an androgen receptor. The specification does not teach how to use the method without an androgen receptor and therefore the androgen receptor is an essential element that is missing from this claim.

Claim 29 recites the limitation "said androgen receptor" in the 2nd line of the claim. There is insufficient antecedent basis for this limitation in the claim, because claim 15 (from which claim 29 depends) does not contain an androgen receptor.

Claim 30 is indefinite because it is unclear where in the method of claim 14 the method step of measuring concentrations will be performed, and also it is unclear how measuring concentrations of said androgen receptor and said Ewing sarcoma protein will lead to the identification required by the preamble of claim 1.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Araya et al, published 2/14/2003 (cited on the IDS submitted 8/4/2004).

Claims 1-9 encompass a method of determining the effect of EWS binding on a derivative of AR. A derivative of AR encompasses any number of changes to the sequence of a human AR, including other nuclear receptors such as the Hepatocyte Nuclear Factor-4 (HNF-4). Araya teaches that EWS enhances HNF4-dependent transcription. Araya further teaches that addition of the molecule CBP further enhances this transcription. Therefore, Araya teaches a method of screening a test substance (CBP) to determine the effect of the test substance on EWS and HNF4 binding, which anticipates claim 1 of the instant invention.

The method of Araya is performed with HEK293 cells, which is an epithelial cell line, which anticipates the further limitations of claims 2-9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Araya et al, published 2/14/2003 (cited on the IDS submitted 8/4/2004) in further view of Brown et al, US 2003/0082511 A1, published 5/1/2003, and claiming priority to 9/25/2001.

The teachings of Araya are summarized above. Araya does not teach a method using nerve cells.

Brown teaches methods of screening for test compounds that modulate target molecules, including nuclear receptors such as HNF-4 (see page 57 and Table 3). Brown further teaches (page 63, paragraph 107) host cells, such as SH-SY5Y nerve cells, which can be used with the methods of the invention.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute SH-SY5Y nerve cells for the HEK293 cells taught by Araya. The person of ordinary skill in the art would be motivated to do so because, in the absence of other evidence, SH-SY5Y nerve cells would work as well as a host cell as HEK293 epithelial cells. The person of ordinary skill in the art would have expected success because Brown teaches SH-SY5Y cells as one of a group of host cell lines, including HEK-293, any of which can be used in the method of screening test compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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